EXHIBIT L

Pharmacokinetics and Drug Interactions: Update for New Antipsychotics

Larry Ereshefsky, Pharm.D., F.C.C.P.

Advances in our understanding of schizophrenia have led to a new generation of antipsychotic agents. These medications not only demonstrate reduced extrapyramidal symptoms but also possess pharmacologic profiles that can be especially advantageous in treating the negative symptoms of schizophrenia. The pharmacokinetics of many of the newer agents are compared and contrasted with typical neuroleptics. Changes in the pharmacokinetics and dosage of the newer agents are also reviewed. A particular emphasis is placed on the metabolism of the newer agents and their potential for drug-drug pharmacokinetic interactions. Clozapine, the archetypal atypical agent, has a complex pharmacokinetic profile with extremely large interpatient variability and many well-documented drug-drug interactions. Thus, clozapine presents special challenges in dose optimization and requires vigilant clinical monitoring for cardiovascular, neurologic, and hematologic adverse effects. Olanzapine demonstrates a very low potential for drug-drug interactions; it requires extremely high inhibitory concentrations at cytrochrome P450 (CYP) systems, typically 30-fold above the usual concentrations observed at steady-state oral high-dose therapy. The metabolic pathways of olanzapine include *N*-glucuronidation, reducing its overall sensitivity to drugs that might induce or inhibit its own metabolism via CYP or flavin-containing monooxygenase (FMO) systems. Plasma olanzapine concentrations at steady state typically demonstrate only a fourfold to fivefold variability among patients at a standard dose of medications. Sertindole and risperidone demonstrate polymorphic metabolism characteristics mirroring the CYP 2D6 phenotype. The inhibitory potentials of sertindole at CYP 2D6 and CYP 3A are modest and not likely to be of clinical significance. However, in those patients taking CYP 2D6 inhibitors or in those who are genotypic poor metabolizers, concentrations achieved by sertindole and its metabolites might result in moderate inhibition of CYP 3A.

(J Clin Psychiatry 1996;57[suppl 11]:12–25)

Recent advances in the neurosciences and clinical sciences have greatly improved our understanding of the neurochemical processes surrounding schizophrenia and psychosis.[1] This greater understanding of schizophrenia has led to a new generation of antipsychotic agents.[2–4] These medications not only demonstrate reduced extrapyramidal symptoms but also possess pharmacologic profiles that can be especially advantageous in treating the negative symptoms of schizophrenia. Determining the appropriate dosage of antipsychotic for a given patient requires the simultaneous integration of several clinically relevant variables including prior treatment history, presenting target behaviors and chronicity of the illness, concurrent medications, comorbid illnesses, and intrinsic variables such as receptor responsivity (physiologic subtypes of the illness). Of these, pharmacokinetic variables and their influence upon dosage are among the most readily understandable and useful.[5] The application of pharmacokinetic principles can improve the utilization of antipsychotic medications and insure their proper clinical use.[6] This paper presents a review of antipsychotic pharmacokinetics, with particular focus paid to the novel agents already approved by the Food and Drug Administration (FDA), e.g., olanzapine, clozapine, and risperidone, and to those drugs pending FDA review and final approval, e.g., sertindole and quetiapine. Definitions of relevant terminology are presented in Table 1.

From the Departments of Pharmacology and Psychiatry, University of Texas Health Science Center at San Antonio, and the College of Pharmacy at The University of Texas at Austin.

Presented at the closed symposium "New Strategies for Treating Psychosis," held January 12, 1996, in Coconut Grove, Florida.

Reprint requests to: Larry Ereshefsky, Pharm.D., University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-6220.

PHARMACOKINETICS AND ITS CLINICAL RELEVANCE

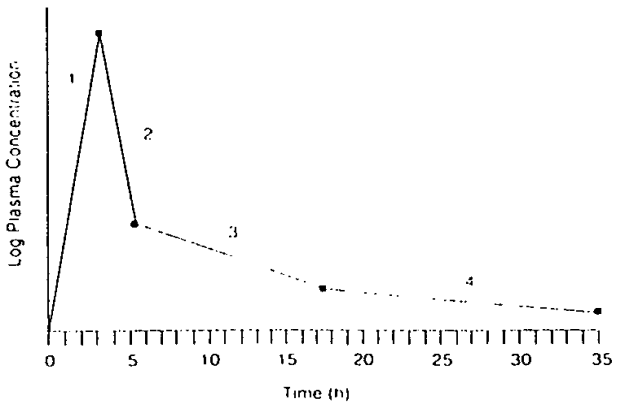
The exponential decay in oral antipsychotic plasma drug concentration (Cp) can be divided into four phases.[7] Figure 1 depicts a typical log-linear plasma concentration versus time curve illustrating absorption (Phase 1), distribution (Phase 2), elimination (Phase 3), and a deep com-

Table 1. Definitions of Pharmacokinetic Terminology*

Pharmacokinetics	the quantitative study and characterization of the time course of drug absorption, distribution, metabolism, and excretion; it is concerned with the relationships of these processes to intensity and time course of therapeutic and adverse effects
Drug absorption	the rate at which the medication enters systemic circulation; for intravenous administration, there is no discernible absorption phase; for depot neuroleptics, the slow absorption rate controls the time for the drug to reach steady state
Bioavailability	F = the fraction of the dose that reaches systemic circulation
Relative bioavailability	$F = \frac{AUC\ p.o.}{AUC\ i.m.}$ if equal doses of drug are given i.m. and p.o., then this ratio defines the dose correction needed to obtain the same Cp over time; AUC is area under the Cp versus time curve
Distribution:	the rate at which a drug moves from the central compartment into peripheral compartments, e.g., tissue
Elimination:	the rate of metabolism for a medication, frequently expressed as the "half-life"; for antipsychotics, this is principally hepatic, though extrahepatic metabolism in the lung and kidneys does occur
Volume of distribution:	Vd is a mathematical measure that allows for Cp to be the basis for modeling of the amount of drug in the body; large Vd denotes marked tissue distribution and binding Amount in body = Vd × Cp
Drug clearance:	a measure of the rate at which the drug is removed from the body
Cp_{max}:	the maximum plasma drug concentration observed
T_{max}:	the time from dosage administration to when Cp_{max} is attained
Steady state:	the equilibrium state reached when the amount of drug administered every day is exactly counterbalanced by the amount of drug eliminated

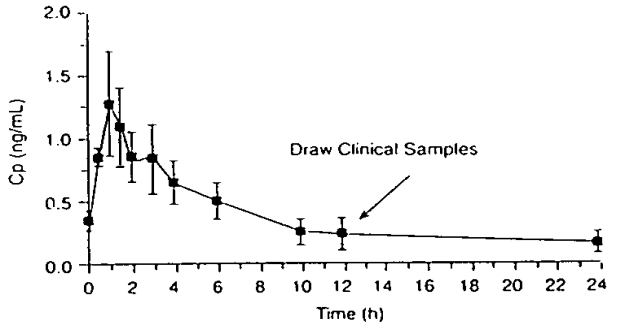
*Abbreviations: AUC = area under the curve; Cp = plasma drug concentration.

Figure 1. Pharmacokinetic Parameters for Oral Antipsychotics *



*From reference 7, with permission. Idealized plasma level versus time curve for a single oral dose of a neuroleptic, illustrating absorption phase (1), distribution into equilibrating compartments (2), metabolic elimination (3), and deep compartment, ususally observed during washout from chronic therapy (4).

Figure 2. Plasma Drug Concentration (Cp) of 10 mg of Fluphenazine Elixir Taken by Mouth b.i.d.



*Data from reference 6.

partment, usually observed during washout from chronic therapy (Phase 4). The first and usually the most rapidly changing phase (defined by the slope of Cp/time) is the absorption phase. Oral liquid dosage forms are more rapidly absorbed than tablets or capsules. Hence, in situations where a rapid response to the antipsychotic is desired, oral liquids can approximate the rate of onset of short-acting intramuscular interventions, as illustrated in Figure 2.[6,8] Alternatively, if a medication possesses potent autonomic system effects, cardiovascular toxicity, or marked sedative properties, then a slower rate of absorption can diminish adverse reactions, e.g., orthostatic hypotension induced by α_1-adrenergic blockade. For the maintenance therapy of schizophrenia, absorption rate is usually not of relevance; rather, the extent of absorption (or the relative bioavailability) and dosage are the significant factors. For the older neuroleptics, high-potency antipsychotic medications such as flupenthixol, fluphenazine, and haloperidol are more rapidly absorbed after intramuscular administration (0.5–1 hour) than by the oral route (2–6 hours) and demonstrate a greater distribution phase.[7] In contrast, chlorpromazine, a low-potency neuroleptic agent, when given intramuscularly, reaches a maximum plasma concentration in 3 to 4 hours. Therefore, the interval between injections used for as needed therapy (i.e., p.r.n.) is, in part, determined by this pharmacokinetic parameter. Higher potency medications can be given more frequently with safety, i.e., every ½ to 1 hour, since the subsequent injection is given close to the peak Cp of the prior injections.[6] This is particularly important as sedation and cardiovascular adverse effects appear to correlate well with plasma concentration within individuals.[9]

Table 2. Comparison of the Pharmacokinetics of Different Antipsychotics[a]

Drug	Bioavailability (%)	Protein-Binding (%)	Vd (L/kg)	t (h)	Active Metabolites	Cp 12 Hours Postdose (ng/mL)
Chlorpromazine	10–33	90–95	7–20	8–35	7-Hydroxy, others	100–300
Thioridazine	25–33	99		9–30	Mesoridazine, sulphoridazine	200–800
Perphenazine	25	90–95	10–35	8–21	None known	0.5–5.0
Fluphenazine	20–50	90–95		14–24	7-Hydroxy (?)	0.2–3.0
Thiothixene	~50	90–95		34	None known	1.0–5.0
Haloperidol	40–70	92	10–35	12–36	Reduced haloperidol	2.0–18.0
Fluphenthixol	40–60	90–93	12–24	22–36	None known	1.0–10.0

[a]Data from references 5 and 11. Abbreviation: Cp = plasma concentration. Symbol ? = questionable activity.

Table 3. Newer Antipsychotics: Comparative Pharmacokinetics[a]

Drug	T_{max} (h)	t (h)	Protein-Binding (%)	Usual Steady State (d)	Oral F (%)	Vd (L/kg)	Metabolites[b]
Clozapine	3.0 ± 1.5	11–105 mean, 16	92–95	4–8	12–81 No Δ food	2–5	Desmethylclozapine ±; clozapine-N-oxide +
Risperidone	1.0–1.5	3–24 mean, 3.6	90	...	~68 Food ↓ rate	1–1.5	9-OH-risperidone + (polymorphism)
Metabolite	3.0	22	70	4–6	...	...	
Olanzapine	5.1 ± 1.2	20–70 mean, 30	93	5–7	> 57[c] No Δ food	10–20	N-glucuronide; 2-OH-methyl; 4'-N-oxide; 4'-N-desmethyl –
Sertindole	10.1 ± 3.0	24–200[c] mean, 55–90; linear at steady state	> 99	7–14	~74 No Δ food	20–40	Dehydrosertindole ± (polymorphism); norsertindole –; hydroxy metabolites ±
Quetiapine	1.0–1.8[d]	6.88	83	1–2	9.0 ± 4.0 Slow ↑ with food	~10	20 metabolites, most inactive; 7-OH-quetiapine +
Ziprasidone	4.7 ± 1.5	4–10 dose dependent	> 99	1–3	59 ↑ with food	2.3	Metabolites "not active" at $D_2/5\text{-}HT_{2A}$

[a]Data from references 12–18 and on file, Abbott Laboratories, 1995.
[b]+ = active; – = inactive; ± = questionable.
[c]Based on urinary recovery data, no i.v. data available, F ≅ 80%.
[c]Outliers due to cytochrome P450 2D6 polymorphism.
[d]Immediate release vs. 5.0 ± 2.4 slow release formulation.

The pharmacokinetic parameters of selected typical neuroleptics are listed in Table 2.[5,6,10,11] The pharmacokinetic properties of atypical antipsychotic agents are summarized in Table 3 (Data on file, Abbott Laboratories, 1995 and references 12–18). Oral absorption, for the most part, is rapid, and food does not significantly affect the pharmacokinetics of absorption for most antipsychotics. Quetiapine and ziprasidone appear to have their absorption increased by food and should be taken consistently with regard to meals. Among the most rapidly absorbed newer agents are risperidone and quetiapine (mean T_{max} = 1–2 hours); both have significant α-adrenergic blockade, which might result in orthostasis if too large a single dose is given. Quetiapine has also been developed in an extended release dosage formulation to slow its rate of absorption. Olanzapine, clozapine, and ziprasidone have intermediate rates of absorption with a mean T_{max} of 3 to 5 hours. Sertindole demonstrates an average T_{max} of 10 hours, which mitigates its potent α_1-adrenergic blockade but reduces its possible effectiveness if given p.r.n. However, the use of adjunctive benzodiazepines has become the preferred approach for the adjunctive management of agitation and aggression, reducing the overall clinical relevance for antipsychotic p.r.n. potential.[19,20] The increased variability in bioavailability demonstrated by clozapine and most lower potency traditional neuroleptics results in a more difficult clinical titration, since there is no single correct dosage or dosage range associated with optimal response. Like many of the newer antipsychotic agents, olanzapine demonstrates an estimated bioavailability of 80% and appears to have more consistent absorption characteristics leading to a more narrow dosing range and simpler dosage titration.

The second component of the Cp versus time curve (Phase 2) is the rapidly declining phase dominated by distribution of the drug from the central compartment and brain back into tissue throughout the body. Since most antipsychotics are extremely fat soluble and highly bound to protein (see Tables 1 and 2), they will rapidly move from blood into tissue, causing the rapidly observed fall in Cp. This distribution effect is clinically significant in that it limits the duration of activity of a single dosage of antipsychotic medication, but is not an important consideration for maintenance therapy. For instance, if a single dose of antipsychotic is administered for agitation, its duration of tranquilizing activity will be brief, typically a

few hours." Additionally, the marked lipophilicity of these agents and their high protein binding indicate that tissue concentrations are greater than plasma concentrations. In the debilitated elderly patient, in those with renal or hepatic disease, or in those patients receiving multiple highly protein-bound medications, reduced doses of antipsychotics should be considered on the basis of pharmacokinetic (protein-binding displacement) and benefit-versus-risk considerations. However, pharmacokinetic studies evaluating drug clearance for olanzapine did not detect significant differences for those patients with severe renal failure. In young, physically healthy patients, protein-binding displacement drug interactions are not usually of significance since increased drug clearance results from the larger unbound or free fraction of drug available for metabolism, self-limiting the interaction. Quetiapine at 83% bound is unlikely to demonstrate protein-binding displacement interactions in at risk patients, since the free fraction is already relatively large.

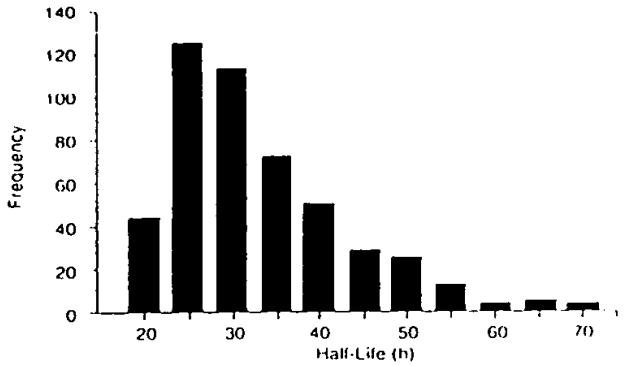
The concentrations of α_1 acid glycoprotein (an acute phase reactant) in plasma show large intraindividual fluctuations, which increase owing to changes in "stress" that disrupt physiologic functions, including depression and schizophrenia.[6,21,22] Therefore, during psychotic exacerbation, or with concomitant medical stressors, the acute phase reactant concentrations increase, binding more antipsychotic drug and resulting in a decreased free fraction and possibly a reduced clinical effect. Conversely, α_1 acid glycoprotein concentrations are diminished in the elderly and in those with cirrhosis. Therefore, depending on the binding characteristics of the medication, plasma concentration ranges determined for therapeutic drug monitoring or during clinical studies evaluating response relationships might not be useful in situations where protein binding is significantly altered. The potential usefulness of free-fraction assays to determine the actual concentration of unbound drug is still unknown, and more research is needed.[18]

The next phase (Phase 3) in Figure 1 represents elimination of the antipsychotic from the body, principally by metabolism. During this log-linear decay phase, the metabolic half-life for the antipsychotic medication can be estimated. The half-life for antipsychotic medications administered by the oral route is typically ≥ 18 hours. Therefore, when subchronic dosing is used, once-daily administration of antipsychotic medication is acceptable since the plasma concentration variation over a 24-hour dosing interval will not be excessively large. Medications such as olanzapine and sertindole can be administered once a day, while quetiapine, risperidone, and clozapine should be given in divided doses.[12–14,16,17,21,23] The ranges documented for metabolic half-lives in Tables 2 and 3 are quite large and primarily reflect the marked differences observed among individuals for metabolic capacity and volume of drug distribution. The observed wide variability in drug clearance for some of these agents indicates a need to more carefully titrate and customize the dosage of the antipsychotic. Additionally, the more cardiotoxic or sedative the agent, the more caution is required, since the margin for error is diminished.

When antipsychotic medications are orally administered on a continuing basis, plasma concentrations are noted to gradually increase over the course of the first 1 to 2 weeks of therapy. This increasing Cp over time can be modeled and predicted by applying the concept of steady state. Steady state is obtained when the amount of drug delivered to the systemic circulation is equal to the amount of drug being eliminated from the body. Therefore, it is an equilibrium state where the input and output functions for drug are balanced. By using the data from Tables 2 and 3, the time required to attain > 90% of steady-state plasma concentrations can be estimated by multiplying the drug half-life times four, or times five to estimate > 98% of steady-state concentrations.[5,6,24] For most antipsychotics administered by the oral route that have an average metabolic half-life of 18 to 36 hours, steady state is attained in approximately 3 to 7 days. However, for sertindole, where the mean metabolic half-life ranges from (study to study) 55 to 90 hours, the time to steady state may be 2 weeks or longer. In a small percentage of patients, the half-life of sertindole can be > 100 hours, resulting in a time to steady state of approximately 3 weeks (Data on file, Abbott Laboratories, 1995 and reference 14). The concept of pharmacokinetic steady state provides additional guidance in the development of clinical dosing guidelines for antipsychotic therapy. Any condition that increases the drug's half-life, e.g., drug interactions or age, will increase the time to steady state by potentially slowing down dose titration. Although pharmacodynamic response lags behind pharmacokinetic considerations for most antipsychotics, if a drug's titration phase to effective doses is limited by adverse effects and/or the rate of drug accumulation in the body, then slow absorption in the case of depot neuroleptics or a long metabolic half-life in the case of sertindole, might delay the achievement of a therapeutic response in CYP 2D6 poor metabolizers.[7,25]

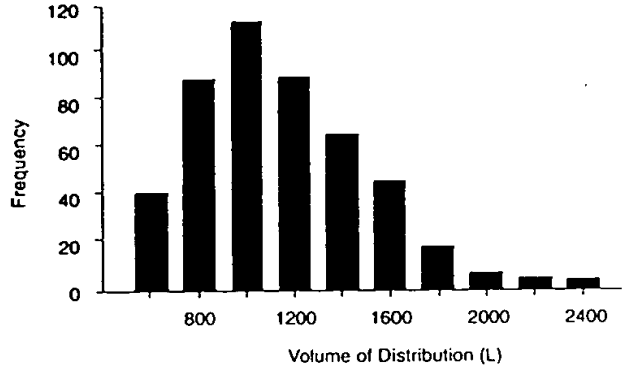
The single most important observation to be made from Tables 2 and 3 is the large variability reported for many of the pharmacokinetic parameters, resulting in up to 30-fold or greater differences in the blood levels resulting from the same dosage of medication administered to a population of patients.[10,16,17,26,27] Most antipsychotics require dosage titration to achieve optimal results, since suggested dosages are the result of efficacy trials dealing with large populations of patients. These data can suggest a likely effective dose, e.g., a dose for which the probability of a successful outcome is greatest, but not an optimum dosage for the individual patient. Figures 3, 4, and 5 illustrate the variability observed for olanzapine's half-life, volume of distribution, and clearance rates for medication taken

Figure 3. Frequency Distribution for Half-Life of Olanzapine*



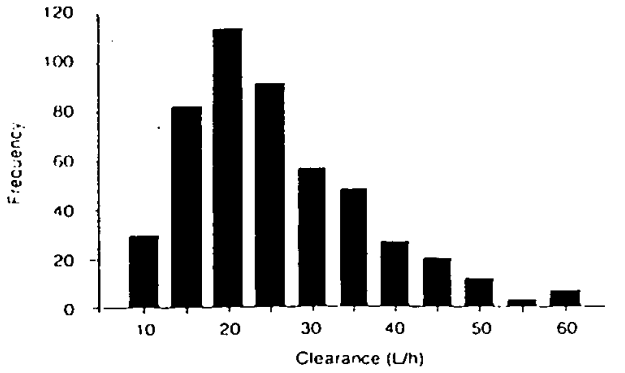
*Data from reference 13.

Figure 4. Overall Frequency Distribution Histogram for Volume of Distribution of Olanzapine*



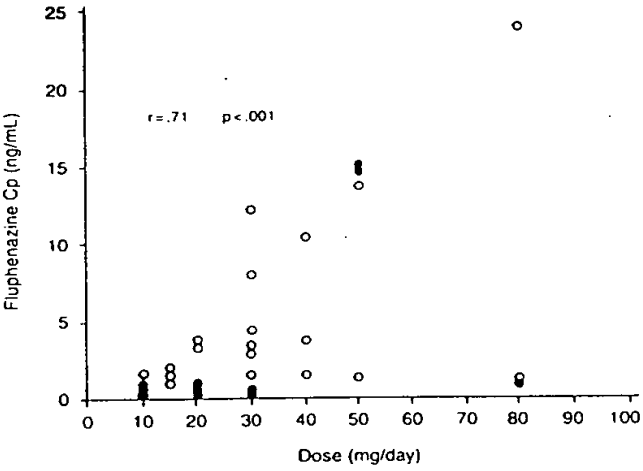
*Data from reference 13.

Figure 5. Overall Frequency Distribution Histogram for Plasma Clearance of Olanzapine*



*Data from reference 13.

Figure 6. Fluphenazine Oral Dosage at Steady State Versus Plasma Concentration (Cp)*



*From reference 6, with permission. Fluphenazine Cp resulting from oral administration of doses of 10–80 mg/day. Twenty-two patients had Cp obtained during therapeutic drug monitoring at San Antonio State Hospital. (Solid circles represent two or more plasma samples at a given dose. Open circles represent single samples.)

orally, respectively. The pharmacokinetics of olanzapine appear to be considerably more consistent from patient to patient than phenothiazine antipsychotics such as oral fluphenazine (Figure 6).[6,7,26] Olanzapine concentrations vary less than fivefold at a standardized dose in clinical efficacy and safety studies.[13] The starting dose of olanzapine, 10 mg/day, is a minimum effective dose for the treatment of schizophrenia, potentially requiring less dosage adjustment than other antipsychotics.

DRUG METABOLISM

The more recently introduced medications have been well characterized with regard to their metabolic pathways and especially the role of cytochrome P450 (CYP).[28–30] Table 4 lists the elimination pathways for clozapine, risperidone, sertindole, and olanzapine (Data on file, Abbott Laboratories, 1995 and references 12–18, 31, 32). The most important pathways for olanzapine metabolism are CYP 1A2, flavin-containing monooxygenase (FMO) 3, and *N*-glucuronidation. Minor pathways include CYP 2D6 and possibly CYP 2C19.[31,32] The CYP 1A2 pathway is associated with a possible ethnic variation in clearance between Japanese and Caucasian subjects, e.g., increased bioavailability for Japanese with increased Cp_{max}, and mean half-lives of 34 versus 24 hours in Caucasians in a preliminary study.[13] Interestingly, CYP 2C19 demonstrates a high degree of polymorphism in Asian populations and might also be implicated in olanzapine metabolism. Similarly, haloperidol demonstrates altered pharmacokinetics in Asians compared with Caucasians and Afri-

Table 4. Elimination Pathways for Selected Antipsychotic Drugs*

Drug	Renal Excretion of Drug	CYP 1A2	CYP 2C	CYP 2D6	CYP 3A	Other Pathways
Clozapine		++ (2C9/10)	+/-	+/-	++	CYP 2E1, FMO
Risperidone				++		
9-OH-risperidone	++					Conjugation
Sertindole				++	++	Fecal excretion
Olanzapine		++ (2C19)	+/-	+		FMO Glucuronidation

*Symbols: ++ = major pathway; + = minor pathway; +/- = possible pathway; - = not a pathway; Abbreviation: FMO = flavin-containing monooxygenase system; CYP = heme-containing cytochrome P450 system.

can-Americans.[33,34] The *N*-glucuronidation of olanzapine is a major pathway (a Phase II oxidative process not involving the CYP system), providing for significant metabolic elimination even if potent inhibitors of drug metabolism are coadministered. Olanzapine and sertindole, like most antipsychotics, are not significantly affected by changes in renal function, and dosing does not appear to be significantly altered in these special populations. Olanzapine clearance, estimated from a population pharmacokinetic study, is affected by aging, which is demonstrated by increased elimination half-lives of 68% in men and 42% in women. The metabolism of clozapine is markedly decreased in the elderly.[35] In contrast, quetiapine and sertindole pharmacokinetics are not significantly altered by the aging process. These differences are thought to be due to the greater susceptibility to the aging process of the CYP 1A2 pathways.

Clozapine appears to demonstrate significant differences in plasma concentrations between men and women (40%–50% increase in women), after controlling for dose and body weight.[36] Similarly, olanzapine demonstrates a statistically significant but more modest increase of approximately 30% in population pharmacokinetic studies.[13] Sertindole demonstrates an approximately 20% reduced clearance rate in women compared with men, though this difference is not likely to be clinically significant, and the clearance rate is comparable once a correction for lean mass is estimated.[14] Preliminary data for risperidone also suggest that plasma concentrations of the 9-OH-risperidone and of the combined concentrations of metabolite and parent are greater in men than in women.[17,37,38] As discussed below, cigarette smoking is an important CYP 1A2 inducer and increases drug clearance for olanzapine, many neuroleptics, and clozapine.

Risperidone and sertindole demonstrate metabolic changes consistent with the CYP 2D6 polymorphism, e.g., a wide range of metabolic capacity, described as a bimodal distribution of extensive and poor metabolizers (Data on file, Abbott Laboratories, 1995 and references 14, 28, 37, 39). In contrast, olanzapine does not demonstrate a significant change in pharmacokinetics in poor versus extensive metabolizers at CYP 2D6, probably due to its multiple metabolic pathways including conjugation and metabolism via the FMO system.[13,33] The ratios of 9-OH-risperidone/risperidone[17,38] and dehydrosertindole/sertindole (Data on file, Abbott Laboratories, 1993 and reference 14) correlate tightly with the dextromethorphan/dextrorphan ratio; however, sertindole has a significant alternative pathway via CYP 3A (producing norsertindole) while risperidone does not. The pharmacologic activity of dehydrosertindole appears to be less than sertindole, possibly increasing the clinical significance of polymorphism and drug interactions at CYP 2D6, though sertindole concentrations are not predictive of therapeutic effects and individualization of dosage is recommended. See the Drug Interactions section for further discussion. The clinical significance of poor versus extensive metabolizer status at CYP 2D6 for risperidone is inadequately evaluated, but likely to be modest, since the combined Cp of risperidone + 9-OH-risperidone stays fairly consistent, and both are pharmacologically active (Data on file, Janssen Research Foundation, 1993 and references 17, 41). However, systematic studies for differences in optimal dosage and side effects have not been completed for risperidone, though in vitro receptor profiles vary somewhat, and protein- and brain-binding characteristics for the two active moieties also differ.[17] Approximately 4% to 10% of Caucasians and a smaller proportion of Asians and Blacks demonstrate a wild-type mutation that results in poor metabolizer status at CYP 2D6.[28]

The metabolic characterization of quetiapine is quite complex; up to 20 compounds have been detected in human and other species, but only 5% have been recovered as the parent drug (Data on file, Zeneca Pharmaceuticals, August 1995 and references 42–44). Metabolic pathways include sulfoxidation (10% of quetiapine), and lesser amounts of the active 7-OH derivative are observed. Although there are potentially two pharmacologically active metabolites, their relative contribution to the total area under the curve (AUC) is small. CYP 2D6 is one of several isoenzymes believed to metabolize quetiapine, though clinical data and drug interaction studies are not available.

Olanzapine, risperidone, clozapine, quetiapine, and many neuroleptics demonstrate dose independent pharmacokinetics over their usual daily oral dosage range. Sertindole clearance decreases with multiple dosing due to an increase in systemic bioavailability (possibly saturation of gastrointestinal mucosal metabolism, a CYP 3A mediated process), resulting in an accumulation of drug to greater Cp than predicted from single-dose studies. However, at steady state, clearance is dose independent, and concentrations are proportional to dose (Data on file, Abbott Laboratories, 1995 and reference 14). These observations,

when coupled with the known genetic polymorphism at CYP 2D6, provide a basis for the reported nonlinearity in the kinetics of sertindole and for the approximately 10% of patients who demonstrate very long plasma half-lives of up to 200 hours (¼ to ⅓ the clearance rate of the general population) and plasma concentrations of sertindole up to threefold greater than the average. The mean half-life in poor metabolizers of sertindole is approximately 130 hours. Ziprasidone demonstrates dose-dependent increases in plasma elimination half-life during steady-state dosing that are not observed during single-dose studies.[21] Due to the short mean half-life of ziprasidone at any dose administered, e.g., 4 hours at 10 mg/day versus 10 hours at 120 mg/day, the clinical significance of this change, though not studied to date, is likely to be small.

The presence of a deep compartment (Phase 4), which might be the rate-limiting kinetic step for the complete washout of the newer antipsychotics upon drug discontinuation from long-term therapy, has not been evaluated. However, it is hypothesized that the increased half-life of ziprasidone at higher daily doses might be the result of an "additional dispositional phase."[23] Most neuroleptics demonstrate a deep compartment as evidenced by urinary metabolite detection up to 3 months after the discontinuation of chronically dosed phenothiazines.[45] Similarly, the deep compartment kinetics of haloperidol taken orally have been characterized in clinical environments, indicating a half-life in excess of 100 hours in case reports.[46] The metabolism of haloperidol is characterized by a reduction step to reduced haloperidol, which is then back oxidized to parent drug (bidirectional), partly explaining this deep compartment.[33,68]

VARIABLES THAT AFFECT CLEARANCE AND RESPONSE TO THERAPY

Drug response, and especially the pharmacokinetics of the traditional neuroleptics are affected by comorbid medical conditions, concurrently administered medications, the aging process, and substance abuse behavior. These variables, listed in Table 5, should be considered when selecting a starting dosage, titration plan, and maintenance dose for an antipsychotic agent. Moreover, if a patient's condition changes during antipsychotic therapy, e.g., concurrent medications are added, then reevaluation of the appropriateness of the dosage is necessary. Aging can reduce hepatic enzymatic function and affect the patient's inherent sensitivity to the medication, thereby resulting in both a pharmacokinetic and pharmacodynamic change in response. For thiothixene, the clearance rates in patients who are > 55 years old cluster at the lower end of the observed range seen in younger patients.[10] The difference in mean clearance rates for thiothixene between younger adults and the elderly is significant: 48.2 L/minute versus 20.0 L/minute. However, the variance for clearance is increased in the elderly, and some patients still require standard doses of neuroleptics to achieve a therapeutic effect. On the average, however, even in those patients without concentration changes due to aging, increased sensitivity for extrapyramidal reactions, autonomic side effects, or orthostatic hypotension can necessitate a 50% or greater reduction in the dose for most elderly patients. Although beyond the scope of this article, drug therapy can be made more cost-effective if the selection of a medication and the optimization of the dosage is based on patient-specific variables.

Many of the newer atypical antipsychotics demonstrate smaller decreases in drug clearance than traditional neuroleptics when they are used in special populations. This difference, when coupled with their reduced propensity to cause extrapyramidal symptoms, should result in safer and less complex drug therapy for the elderly and for those patients with hepatic dysfunction. Table 6 summarizes dosing adjustment recommendations suggested for the elderly and for those patients with significant renal or hepatic disease (Data on file, Abbott Laboratories, 1995; Data on file, Zeneca Pharmaceuticals, August 1995 and references 13–15, 17, 18, 47). Sertindole and quetiapine demonstrate no significant differences in their pharmacokinetics when the elderly are compared with younger adults. Olanzapine demonstrates a modest, statistically significant, decrease

Table 5. Variables That Influence the Pharmacokinetics of Antipsychotics

Age
Elderly patients demonstrate greater variability in drug clearance
The "super-elderly" (those greater than 80 years of age) demonstrate the most consistent reduction in clearance rates
Genetics
Polymorphism at CYP 2D6 and CYP 2C19
Wide interpatient variability at CYP 3A
Ethnic differences in metabolism
Substance abuse behaviors
Cigarette smokers demonstrate increased metabolic capacity, CYP 1A2
Ethanol abusers can demonstrate increased or diminished metabolic capacity dependent on the extent of their drinking behavior and their hepatic and nutritional status
Medical conditions
Decreased hepatic blood flow can reduce clearance, e.g., congestive heart failure
Hepatic disease such as cirrhosis and hepatitis can decrease clearance
Enzyme inducers
Carbamazepine, phenytoin, ethambutol, barbiturates
Clearance inhibitors
Examples include: serotonin selective reuptake inhibitors, tricyclic antidepressants, cimetidine, β-blockers, isoniazid, methylphenidate, erythromycin, triazolobenzodiazepines, chloramphenicol, ciprofloxacin, ketoconazole, and many others
Changes in binding proteins
Stress (acute phase reactants increase) such as α_1 acid glycoprotein increase
Hypoalbuminemia can occur with malnutrition or hepatic failure
Changes in protein binding occur due to hepatic or renal failure

Table 6. Changes in Pharmacokinetics: Special Populations[a]

Drug	Elderly	Renal	Hepatic	Ethnic
Clozapine	↓↓ dose	No Δ dose	↓ dose	↓ dose women ↓ dose Asians[b]
Risperidone	↓↓ dose	↓ dose	↓ dose[b]	CYP 2D6 polymorphism
Olanzapine	↓ dose (35%) PD concerns	No Δ dose	No Δ dose (preliminary)	↓ dose women ↓ dose Asians[b]
Sertindole	No Δ dose PD concerns	No Δ dose	↓ dose[b]	↓ women CYP 2D6 polymorphism
Quetiapine	No PK Δ[b] ↓ Dose ?[b] PD	No Δ	Slight ↓ dose	?

[a]Data from references 12–18 and on file, Abbott Laboratories, 1995.
Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic.
[b]Increased adverse reactions (or blockade).

in clearance rates with age. However, all of these drugs should be dosed more cautiously in the elderly owing to the potential for increased adverse reactions secondary to pharmacodynamic changes in neuronal systems and homeostasis.[5] Note that risperidone and clozapine dosing should be considerably more conservative in the elderly, in part because of substantial pharmacokinetic changes associated with diminished hepatic capacity, but also due to the increased rate of orthostatic hypotension and syncope observed if standard adult doses are utilized.

Drug Interactions

Drug-drug interactions can have a significant effect on the pharmacokinetics of antipsychotic agents and upon appropriate dosage. Reduction of antipsychotic Cp can occur through the use of microsomal CYP-inducing anticonvulsant medications (CYP 3A and possibly CYP 2B), particularly carbamazepine,[48,49] phenobarbital, phenytoin,[50] and from any other drug or condition that might induce microsomal enzymes, such as moderate routine ethanol consumption (CYP 2E1 and possibly others) or cigarette smoking (CYP 1A2). Thioxanthenes, such as thiothixene, appear to be extremely sensitive to changes in metabolic clearance secondary to drug interactions.[10] For typical neuroleptics, there is usually a greater than twofold increase in clearance rate if anticonvulsants such as carbamazepine are coadministered. This means that it will require twice as much medication to achieve the same Cp during the drug interaction than without the coadministered medication. In the presence of these medications, doses of sertindole (CYP 3A substrate) might need to be up to 50% greater.[14] Similarly clozapine doses might need to be increased, though enzyme-inducing anticonvulsants are not recommended for coadministration since hematologic toxicity might be enhanced.[18,47,51,52] Olanzapine and risperidone, in contrast, are unlikely to be affected by carbamazepine, though monitoring of patients for exacerbation is prudent.[17,31]

Alternately, patients receiving SSRIs, ketoconazole, cimetidine, tricyclic antidepressants, β-blockers such as propranolol, and some antibiotics including erythromycin and chloramphenicol can exhibit a clearance rate for traditional neuroleptics that is less than one half of that observed in the group not taking drugs that interact with traditional neuroleptics.[10,15,29,30] In a "worst case scenario" where a patient is switched from an enzyme-inducing to an enzyme-inhibiting medication, a greater than fourfold shift in drug metabolism might occur. Clozapine interactions appear to occur at both the CYP 1A2 and CYP 3A systems.[35] Clozapine toxicity has been reported after the coadministration of erythromycin.[53] It is important to note that drug interactions are bidirectional. Antipsychotics can also inhibit the metabolism of coadministered medications, e.g., haloperidol inhibition of tricyclic antidepressant metabolism.[22,45] Recently, a case report suggested that nortriptyline Cp was increased secondary to clozapine therapy, resulting in an anticholinergic delirium.[54]

Drug interaction studies are required for the approval of new medications. Tables 7, 8, and 9 list currently available information regarding potential drug interactions for clozapine,[18,35,47,51-54] sertindole (Data on file, Abbott Laboratories, 1995 and reference 14), and olanzapine,[13,31,32] respectively. From these data, potential drug-drug interactions of clinical significance affecting the clearance of the antipsychotic *might* result at the CYP 2D6 and CYP 3A systems for sertindole; at CYP 1A2, CYP 3A, and FMO (flavin monooxygenase) systems for clozapine, and at the CYP 1A2 and at FMO3 systems for olanzapine. Conversely, sertindole appears to inhibit CYP 2D6 (IC_{50} estimated to be between 1.25–2 μM) and weakly inhibit the CYP 3A systems (IC_{50} estimated to be about 200 μM for sertindole, 50 μM for dehydrosertindole, and ~25 μM for norsertindole). There appears to be only a modest potential to cause increased concentrations of coadministered medications that are substrates at these systems. It is estimated that typical steady-state concentrations of sertindole at 20 mg/day are 0.16 μM/mL, well under the listed IC_{50}. However, metabolite concentrations can be considerably greater than parent drug concentrations and potentially can increase drug interaction potential. At CYP 2D6, dextromethorphan metabolism (probe for system) is modestly decreased, as evidenced by a shift in the urinary ratio of dextromethorphan/dextrorphan from 0.006 to 0.015. This ratio shift is an order of magnitude less than would typically occur with fluoxetine or paroxetine when similar dextromethorphan probe methodology is used.[28-30] To further illustrate, terfenadine concentrations demonstrated a mean increase of only 28% in patients receiving 20 mg/day of sertindole and a single 120-mg dose of terfenadine (Data on file, Abbott Laboratories, 1995). Clinically significant reactions require changes of 500% to 1000% in terfenadine Cp. The potential for drug interactions at CYP 3A are likely to be modestly increased when drugs that significantly inhibit CYP 2D6 are coadministered since sertindole concentrations are approximately threefold in-

Table 7. Drug Interactions Affecting Clozapine*

Drug	Effect	Enzyme Selectivity	Lowest IC_{50} and/or Clinical Data	Significance
Diazepam	CNS sedative	CYP 2C19, CYP 3A	No pharmacokinetic changes	High
Ketoconazole, erythromycin	Inhibitor	CYP 3A	9.7 μM Case of seizures	Moderate: elevated clozapine levels
Carbamazepine, phenytoin	Inducer	CYP 3A	Cases of psychotic exacerbation	Moderate: decreased clozapine levels
Furafylline, thioridazine	Inhibitor	CYP 1A2	3.6 μM Case reports of toxicity, improved negative symptoms	High: elevated clozapine levels > 3–7 fold
Cigarette smoke	Inducer	CYP 1A2	Lowers plasma concentrations proportional to number of cigarettes smoked	Moderate: decreased clozapine levels
Sulfaphenazole	Inhibitor	CYP 2C9/10	58.4 μM	Low: minor pathway inhibition
Quinidine, risperidone†	Inhibitor	CYP 2D6	153.1 μM Case report of increased plasma concentration	Low: minor pathway inhibition possible
p-Nitrophenol, ethanol	Inhibitor	CYP 2E1	44.6 μM	Low to moderate
Cimetidine	Inhibitor	Multiple systems and reduces hepatic blood flow	Clinical case of seizures with increased plasma levels	Low to moderate: multiple systems involved
Fluoxetine	Inhibitor	Potent at CYP 2D6 and CYP 2C, modest effects at CYP 3A, weak effect at CYP 1A2	Clinical cases of moderate change in plasma levels and seizures reported to occur	Low to moderate: multiple systems involved, possibly only relevant at higher doses

*Data from references 18, 35, 47, 51–54.
†In vitro data do not support inhibition at CYP 2D6.

Table 8. Drug Interactions Affecting Sertindole*

Drug	Effect	Enzyme Selectivity	In Vitro and/or Clinical Data	Significance
Erythromycin, calcium channel blockers	Inhibitor	CYP 3A	200 μM = 100% inhibition Modest elevations of sertindole possible	Low to moderate: probably only significant if patient is CYP 2D6 poor metabolizer
Ketoconazole, itraconazole	Inhibitor	CYP 3A	2 μM = 100% inhibition Significant elevations of sertindole likely to occur	Moderate to high: more significant if patient is CYP 2D6 poor metabolizer
Carbamazepine, phenytoin	Inducer	CYP 3A	Large decreases in plasma levels of from 2.2- to 3.4-fold	High: decreased sertindole levels, consider higher doses
Cigarette smoke	Inducer	CYP 1A2, weak effects on CYP 3A??	Modestly lowers plasma concentrations (< 25%) despite absence of CYP 1A2 pathway for sertindole	Low: no dosage change likely to be needed
Quinidine,† paroxetine	Inhibitor	CYP 2D6	Moderately increased plasma concentrations (2- to 3-fold) in extensive metabolizers	Moderate: dose reductions might be considered
Cimetidine	Inhibitor	Multiple systems and reduces hepatic blood flow	Likely to increase sertindole concentrations by 50%	Low to moderate: multiple systems involved
Fluoxetine	Inhibitor	Potent CYP 2D6,and CYP 2C, modest effects at CYP 3A, weak effect at CYP 1A2	Moderate increases in plasma concentrations (2- to 3-fold) at 20 mg/day‡	Moderate to high: multiple systems involved, increasing interaction risk above paroxetine

*Data on file, Abbott Laboratories, 1995 and from reference 14. Symbol: ?? = possible effect.
†Due to the potential for QT_c prolongation, quinidine and sertindole should not be coadministered.
‡Likely to be fluoxetine dose dependent.

creased. Similarly, those patients who are genotypic poor metabolizers at CYP 2D6 might also demonstrate an increased risk for drug interactions. European labeling for sertindole suggests that clinically relevant interactions could occur in selected subpopulations of patients.[14]

In contrast, olanzapine does not appear to significantly inhibit any of the studied CYP isoenzymes.[31,32] The usually achieved concentration of olanzapine at 17.5 mg/day is ≤ 0.5 mm. By using the hydroxylation of midazolam as an in vitro probe, the K_i (μM) at CYP 3A4 for keto-

Table 9. Drug Interactions Affecting Olanzapine*

Drug or Metabolic Condition	Effect	Enzyme Selectivity	In Vitro and/or Clinical Data	Significance
Ethanol	Inhibitor and CNS sedative	CYP inhibitor	Slight increase in olanzapine absorption (< 25%), pharmacodynamic effect noted	Moderate to high: avoid ethanol; increased somnolence and orthostatic hypotension potentiated
Diazepam	CNS sedative	CYP 2C19, CYP 3A	No pharmacokinetic changes	Moderate: increased somnolence and potentiated orthostatic hypotension, use with caution and at lower doses
Carbamazepine, phenytoin†	Inducer	CYP 3A	Moderate decreases in plasma levels (≤ 50%)	Low: decreased olanzapine levels of doubtful clinical importance but might require dose increase in selected patients
Ketoconazole, erythromycin	Inhibitor	CYP 3A	No changes in kinetics reported	Low: until further experience is obtained, monitor patients at standard doses for increased effect
Cigarette smoke	Inducer	CYP 1A2	Moderately lowers plasma concentrations (33% increase in oral clearance)	Moderate: decreased olanzapine levels might require dosage increase
Fluvoxamine	Inhibitor	CYP 1A2	Likely to increase plasma concentrations, though no reports	Moderate: monitor patients for exacerbation of psychosis, might need dosage increase
Poor versus extensive metabolizers	...	CYP 2D6	No differences in pharmacokinetics observed	No adjustments likely with inhibitors
Cimetidine	Inhibitor	Multiple systems and reduces hepatic blood flow	Likely to increase olanzapine concentrations	Low to moderate: multiple systems involved

*Data from references 13, 31, 32.
†Case of diminished efficacy after phenytoin administration required dose increase to 25 mg/day of olanzapine (Ereshefsky L. Unpublished data.)

conazole was 0.11, for clozapine was 99, and for olanzapine was 491. These results suggest that there should be less than a 1% inhibition of midazolam metabolism by either olanzapine or clozapine. At CYP 2D6, when 1′-hydroxy-bufarol was used, the in vitro K_i (μM) for quinidine was 0.03, for clozapine was 19, and for olanzapine was 89. In contrast to the potent inhibitory effect of quinidine and the modest effect for clozapine (clozapine concentrations are typically 1–2 μM), olanzapine should not significantly interact with CYP 2D6. Similarly, at both CYP 2C9 and CYP 2C19, when tolbutamide and S-mephenytoin are used as in vitro probes, respectively, olanzapine was expected to result in less than a 1% inhibition of metabolism at these systems. Clozapine similarly demonstrated a weak potential to interact at CYP 2C9, inhibiting in vitro metabolism by < 5%. Cautious extrapolation of in vitro results to patients should be exercised. Metabolite contributions to CYP inhibition, and the possible effects from patients with higher than usual concentrations have not been fully evaluated for the newer antipsychotics. Clinical and in vitro studies evaluating drug interactions at the FMO system for olanzapine have not been reported. FMO substrates such as cimetidine (S-oxide formation) and tamoxifen (N-oxides) might inhibit olanzapine metabolism, though the converse is unlikely given the high K_m of olanzapine for N-oxidation.[31,32] In vivo studies with olanzapine demonstrating no significant changes in the pharmacokinetics for coadministered medications include warfarin, imipramine, carbamazepine, diazepam, ethanol (increased sedative effects noted without pharmacokinetic differences), and theophylline.[13]

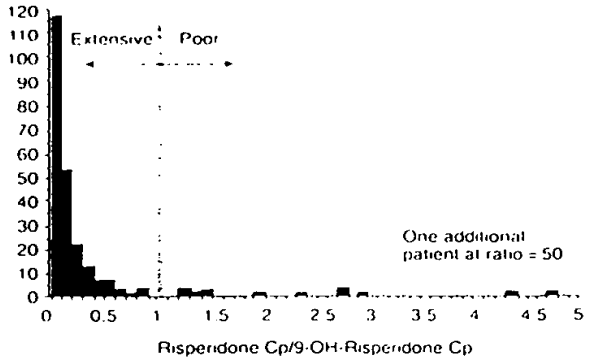
Drug interactions affecting risperidone pharmacokinetics have also been evaluated and are considered unlikely to be highly clinically significant, due to the 9-OH-risperidone's nearly comparable efficacy to the parent compound. Nonetheless, paroxetine and fluoxetine will convert ≥ 50% of patients to poor metabolizer status at CYP 2D6,[30] potentially inverting the ratio for 9-OH-risperidone/risperidone[39] and for dehydrosertindole/sertindole (Data on file, Abbott Laboratories, 1995). Other medications, including low-potency phenothiazines and quinidine can also inhibit CYP 2D6 significantly and should also shift the metabolic ratio of risperidone (Data on file, Janssen Research Foundation, 1993). In poor versus extensive metabolizers, identified by phenotype screening under drug-free conditions, there is a dramatic difference in the pharmacokinetic profile of risperidone and the 9-OH metabolite (see Table 10).[17,39] As Figure 7 demonstrates, in a population of patients in a phase 3 risperidone efficacy and safety trial, an extremely large range for the risperidone/9-OH-risperidone Cp ratio was determined.[38] The clinical significance of the pharmacokinetic and pharmacodynamic effects of these possible interactions requires further study since CNS binding properties, plasma protein binding, and moderate differences in adrenergic receptor blocking potencies for the two active moieties have been documented.[17] Increased clinical monitoring is appropriate when CYP 2D6 inhibitors are

Table 10. Pharmacokinetics of Risperidone by Debrisoquine Metabolizer Status*

Measurement	Metabolizer: Extensive	Intermediate	Poor
Dextromethorphan metabolite ratio	0.0002–0.015	0.12	5.4 & 6.88
Vdss (L/kg)	1.1 ± 0.2	2.1	1.1 ± 0.5
Clearance (mL/min/kg)	5.4 ± 1.4	2.8	0.74 ± 0.15
Risperidone half-life (h)	2.8 ± 0.5	10.2	21.0 ± 5
9-OH-Risperidone half-life (h)	20–22	20–22	20–22
AUC ratio 9-OH-Risperidone/risperidone	2.9 ± 0.7	0.5	0.20 ± 0.00

*Data from references 7 and 39. Abbreviation: AUC = area under the curve.

Figure 7. Histogram Demonstrating Possible Poor Metabolizers of Risperidone*



*Data from reference 38.

added or subtracted from risperidone, especially in the elderly and debilitated patient. Alternately, no potent inhibition of risperidone metabolism was observed for compounds that interact with CYP 1A1, CYP 1A2, CYP 2C9, CYP 2C19, and CYP 3A4 (Ereshefsky L, Anderson C, Clyde C. 1993. Unpublished data). Risperidone does not appear to significantly inhibit any of the CYP systems studied in vitro, though a recent report in which a patient demonstrated increased clozapine levels subsequent to risperidone coadministration highlights the need for human studies and the cautious extrapolation of in vitro data to the clinical environment (Ereshefsky L, Anderson C. 1993. Unpublished data; Data on file, Janssen Research Foundation, 1993 and references 18, 37, 41). Ziprasidone drug interaction data are not readily available at this point in the drug development process. However, a recent study reported no significant change in metabolic clearance for ethinyl estradiol and levonorgestrel (combination oral contraceptive) during ziprasidone coadministration. A slight reduction in T_{max} for ethinyl estradiol was noted during ziprasidone therapy, but this is not considered clinically significant.[15]

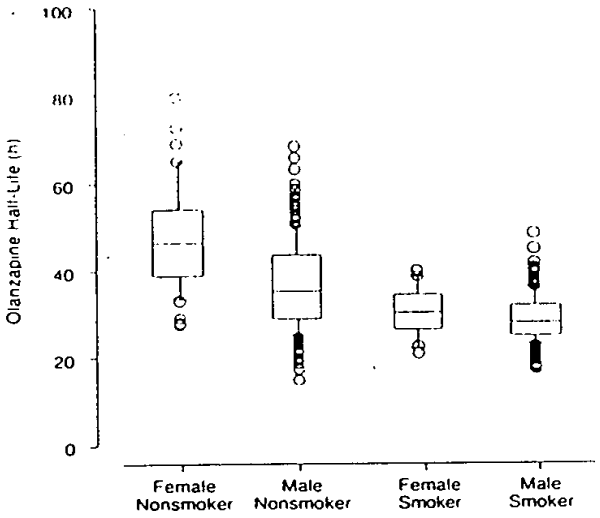
Although most drug interactions simply require increased clinical monitoring and dosage adjustment, the potential for significant interactions should prompt greater vigilance, especially for newly introduced antipsychotic agents. The most well-publicized, potentially life-threatening interactions are reported to occur at CYP 3A. Substrates at this system include terfenadine, astemizole, and cisapride, drugs that are associated with cardiotoxicity and life-threatening arrhythmias when they are coadministered with potent CYP 3A inhibitors such as ketoconazole and erythromycin. The relative risk of moderately potent inhibitors at CYP 3A is currently of great interest, since ketoconazole, erythromycin, nefazodone, and fluvoxamine are labeled as contraindicated with these three CYP 3A-metabolized drugs.[29,30] On the basis of in vitro data for sertindole at CYP 3A, it is unlikely for a clinically significant interaction to occur with astemizole, cisapride, and terfenadine. Nonetheless, a possible scenario for caution in a patient on sertindole treatment might be when a patient is coadministered CYP 2D6 inhibitors or is a poor metabolizer by genotype (sertindole and norsertindole concentrations would be elevated), *and* the patient is also on additional medications that each have moderate inhibitory effects on CYP 3A (e.g., calcium channel blockers, tricyclic antidepressants). This extrapolation from existing data requires verification.

Cigarette Smoking

An important environmental influence on antipsychotic drug clearance is cigarette smoking, including passive inhalation of smoke.[10,55,56] Depending upon the antipsychotic medication, changes in Cp of from 20% to 100% can be observed when smoking status changes in a patient. For instance, cigarette smokers, on average, have a 25% to 50% faster metabolic rate for thiothixene than nonsmokers, while data for fluphenazine, both as the oral and depot formulations, demonstrate nearly a 100% increase in clearance rates.[56] Haloperidol clearance is also increased by 50% or more. The greatest impact of smoking on plasma concentrations of haloperidol occurs within the therapeutic range, while at high doses, e.g., ≥ 50 mg/day, the effect of smoking on clearance is diminished owing to metabolic saturation. Alternately, if a patient ceases smoking while maintaining a constant dose of antipsychotic medication, increased adverse events can occur.[57]

Olanzapine's metabolism to the N-desmethyl and 7-OH derivatives is principally via CYP 1A2. Therefore, it is not surprising that cigarette smoking significantly increases the clearance rate for olanzapine. Figure 8 depicts half-lives for olanzapine at steady state stratified for both cigarette smoking and gender.[13] An approximate 50% decrease in the half-life of olanzapine is observed for smoking versus nonsmoking patients of the same gender. Corresponding increases in clearance, principally the result of a faster elimination rate, suggest that aryl hydrocarbon exposure (from smoke) has induced CYP 1A2. Interestingly, sertin-

Figure 8. Olanzapine Half-Life Distribution by Smoking and Gender*



*Data from reference 13.

dole clearance rates are increased approximately 14% to 17% in tobacco smokers compared with nonusers, despite the absence of a major metabolic pathway via CYP 1A2 (Data on file, Abbott Laboratories, 1995).

Antipsychotic Plasma Concentration Versus Response Relationships

Haloperidol and fluphenazine have sufficient data to suggest a therapeutic range of plasma concentrations for optimal benefit while minimizing adverse effects. The therapeutic window for haloperidol has been substantiated in several studies, and depending on assay accuracy, is considered to range from 3 to 15 ng/mL.[1,58-63] Fluphenazine appears to have more of a linear relationship of concentration and response, but demonstrates dose-limiting adverse effects toward the upper end of the therapeutic range (0.3–2.5 ng/mL).[8,63-66] Logistic regression analysis for both a therapeutic effect and for side effects yielded a fluphenazine Cp of 0.69 ng/mL for best response without disabling side effects. At Cp ≥ 2.7 ng/mL, 90% of patients will have "disabling" side effects. Note that at Cp > 0.69 ng/mL, greater improvement in psychotic symptoms is attained but at the expense of side effects. Therefore, a benefit-to-risk assessment must be made as higher doses (levels) are used.

Clozapine concentrations appear to be potentially useful in the treatment of patients with refractory schizophrenia. Parent drug Cp of ≥ 350 ng/mL have been suggested to be indicative of an adequate trial on clozapine and to distinguish responders from nonresponders.[67] A confirming study suggested a discriminant cutoff was observed at 375 ng/mL, and that cigarette smoking necessitated increased doses of clozapine.[13] However, not all studies find a correlation of response with concentration.[68] It has also been suggested that increased concentrations of desmethylclozapine might increase the risk of agranulocytosis.[69] For most of the newer antipsychotics, no obvious plasma concentration versus response relationship emerges from phase 2 and phase 3 efficacy trials. For instance, risperidone does not demonstrate a statistically significant linear or curvilinear plasma concentration relationship for overall clinical improvement, response to negative symptoms, or for extrapyramidal symptom occurrence. However, these trials were not designed to properly assess concentration versus response issues. Interestingly, prolactin concentrations significantly correlated with risperidone + 9-OH-risperidone and with 9-OH-risperidone Cp. (Ereshefsky L, Anderson C, Clyde C. 1993. Unpublished data and references 37, 41). Further research is needed to convincingly address this clinically important issue.

CONCLUSION

Clozapine, the archetypal atypical agent, has a complex pharmacokinetic profile with extremely large interpatient variability and many well-documented drug-drug interactions. This presents special challenges in dose optimization and requires vigilant clinical monitoring for cardiovascular, neurologic, and hematologic adverse effects. Olanzapine demonstrates a very low potential for drug-drug interactions, requiring extremely high inhibitory concentrations at cytrochrome P450 systems, typically 30-fold or greater above the usual concentrations observed at steady state on oral high-dose (17.5 mg/day) therapy. Olanzapine's metabolic pathway includes *N*-glucuronidation, reducing its overall sensitivity to drugs that might induce or inhibit its own metabolism via CYP. Olanzapine concentrations at steady state typically demonstrate only a fourfold variability among patients at a standard dose of medications. Dose reductions in special populations are necessary when two or more factors affecting dose are present, e.g., 50% dose reduction to 5 mg/day if an elderly nonsmoking woman is started on olanzapine. Sertindole and risperidone demonstrate polymorphic metabolism characteristics mirroring the CYP 2D6 phenotype. Sertindole's inhibitory potentials at CYP 2D6 and CYP 3A are modest and not likely to be of clinical significance. However, in those patients taking CYP 2D6 inhibitors, or genotypic poor metabolizers, concentrations of sertindole and its metabolites might result in moderate inhibition of CYP 3A.

The application of pharmacokinetic principles can assist the clinician to improve the monitoring plan for patients with schizophrenia. Moreover, patient-specific data including gender, cigarette smoking, age, concurrent

drugs, and comorbid diseases should influence the starting dose, the rate of dose titration, and the anticipated maintenance dose for the antipsychotic. Although plasma concentration versus response relationships are not established for most antipsychotics (with the possible exception of clozapine, haloperidol, and fluphenazine), optimization of dosage based on consideration of pharmacokinetic factors should improve the outcomes of therapy for the patient with schizophrenia.

Drug names: astemizole (Hismanal), carbamazepine (Tegretol and others), chloramphenicol (Pantofenicol), chlorpromazine (Thorazine and others), cimetidine (Tagamet), ciprofloxacin (Cipro IV), cisapride (Propulsid), clozapine (Clozaril), diazepam (Valium and others), erythromycin (Erymax and others), ethambutol (Myambutol), ethinyl estradiol (Diogyn E and others), fluoxetine (Prozac), fluphenazine (Prolixin and others), fluvoxamine (Luvox), haloperidol (Haldol and others), imipramine (Trofranil and others), ketoconazole (Nizoral), levonorgestrel (Norplant), methylphenidate (Ritalin), midazolam (Versed), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), phenobarbital (Nembutal and others), phenytoin (Dilantin and others), propranolol (Inderal and others), quetiapine (Seroquel), quinidine (Duraquin and others), risperidone (Risperdal), sertindole (Serlect), sulfaphenazole (Sulfabid), tamoxifen (Nolvadex), terfenadine (Seldane), theophylline (Theocin and others), thioridazine (Mellaril and others), thiothixene (Navane), tolbutamide (Orinase), warfarin (Coumadin and others).

REFERENCES

1. Ereshefsky L. Treatment strategies for schizophrenia. Psychiatric Annals 1995;25:285–296
2. Ereshefsky L, Tran-Johnson T, Watanabe MD. Current concepts in the treatment of schizophrenia: the pathophysiologic basis for atypical antipsychotic efficacy. Clin Pharm 1990;8:680–707
3. Goldstein JM. Pre-clinical pharmacology of new atypical antipsychotics in late stage development. Exp Opinion Invest Drugs 1995;4:291–298
4. Kinon BJ, Lieberman JA. Mechanism of action of atypical antipsychotic drugs: a critical analysis. Psychopharmacology (Berl) 1996;124:2–34
5. Ereshefsky L, Richards A. Psychosis. In: Koda-Kimble MA, Young LL, eds. Applied Therapeutics: The Clinical Use of Drugs. San Francisco, Calif: Applied Therapeutics Press; 1992
6. Ereshefsky L, Jann MW, Saklad SR, et al. Bioavailability of psychotropic drugs: historical perspective and pharmacokinetic overview. J Clin Psychiatry 1986;47:6–15
7. Ereshefsky L, Saklad SR, Jann MW, et al. Future of depot neuroleptic therapy: pharmacokinetic and pharmacodynamic approaches. J Clin Psychiatry 1984;45(5, sec 2):50–59
8. Ereshefsky L, Saklad SR, Davis CM, et al. Pharmacokinetics of fluphenazine by high performance thin layer chromatography [abstract]. Drug Intelligence and Clinical Pharmacy 1983;17:436
9. Saklis G, Curry SH, Mould GP, et al. Physiologic and clinical effects of chlorpromazine and their relationship to plasma level. Clin Pharmacol Ther 1972;13:931–946
10. Ereshefsky L, Saklad SR, Watanabe MD, et al. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. J Clin Psychopharmacol 1991;11:296–301
11. Balant-Gorgia AE, Balant L. Antipsychotic drugs: clinical pharmacokinetics of potential candidates for plasma concentration monitoring. Clin Pharmacokinet 1987;13:65–90
12. Wong YWJ, Ewing BJ, Fabre LF, et al. Multiple-dose pharmacokinetics of quetiapine in male schizophrenic patients. Presented at the Collegium Internationale Neuro-Psychopharmacologicum; June 1996; Melbourne, Australia
13. Eli Lilly and Co. New drug application no. 20-592. 1996;96:1–347
14. Lundbeck Limited. Summary of product characteristics, Serdolect®. United Kingdom; 1996
15. Muirhead GJ, Holt GJ, Harness OS, et al. The effect of ziprasidone on steady-state pharmacokinetics of combined oral contraceptives. Presented at Collegium Internationale Neuro-Psychopharmacologicum, June 1996, Melbourne, Australia
16. Chee MG, Hsuan F, Hongfeld G, et al. Single vs multiple dose pharmacokinetics of clozapine in psychiatric patients. Pharm Res 1990;7:347–351
17. Ereshefsky L, Lacombe S. Pharmacological profile of risperidone. Can J Psychiatry 1993;38(3, suppl):S80–S88
18. DeVane CL. Drug interactions and antipsychotic therapy. Pharmacotherapy 1996;16(suppl):15S–20S
19. Ward ME, Saklad SR, Ereshefsky L. Lorazepam in treatment of psychotic agitation [letter]. Am J Psychiatry 1986;143:1195
20. Arana GW, Ornsteen ML, Kauter F, et al. The use of benzodiazepines for psychotic disorders: a literature review and preliminary clinical findings. Psychopharmacol Bull 1986;22:77–90
21. Verghese C, Kessel JB, Simpson G. Pharmacokinetics of neuroleptics. Psychopharmacol Bull 1991;27:551–563
22. Ereshefsky L, LeRoy A, Tran-Johnson T, et al. Pharmacokinetic factors affecting antidepressant drug clearance and clinical effect: evaluation of doxepin and imipramine—new data and review. Clin Chem 1988;34:863–880
23. Wilner KD, Hansen RA, Johnson AC, et al. Single and multiple dose pharmacokinetics of ziprasidone in healthy males. Presented at the Collegium Internationale Neuro-Psychopharmacologicum; June 1996; Melbourne, Australia
24. Gibaldi M, Perrier D. Pharmacokinetics. In: Drugs and the Pharmaceutical Sciences, vol 15. New York, NY: Marcel Dekker; 1982:1–60
25. Ereshefsky L, Saklad SR, Tran-Johnson T, et al. Kinetics and clinical evaluation of haloperidol decanoate loading dose regimen. Psychopharmacol Bull 1990;26:108–114
26. Ereshefsky L, Saklad SR, Davis CM, et al. Clinical implications of fluphenazine kinetics. Presented at the American Psychiatric Association; 1984; New York, NY
27. Hasegawa M, Gutierrez-Estinou R, Way L, et al. Relationship between clinical efficacy and clozapine concentrations in plasma in schizophrenia: effect of smoking. J Clin Psychopharmacol 1993;13:383–390
28. Ereshefsky LE, Riesenman C, Lam YWF. Antidepressant drug interactions and the cytochrome P450 system: the role of CYP2D6. Clin Pharmacokinet 1995;29(suppl):10–19
29. Ereshefsky L, Riesenman C, Lam YWF. Serotonin selective reuptake inhibitor drug interactions and the cytochrome P450 system. J Clin Psychiatry 1996;57(8, suppl):17–25
30. Ereshefsky L. Drug-drug interactions involving antidepressants: focus on venlafaxine. J Clin Psychopharmacol 1996;16(suppl):37–53
31. Ring BJ, Catlow J, Lindsay TJ, et al. Identification of the human cytochrome P450 responsible for the in vitro formation of the major oxidative metabolites of the antipsychotic agent olanzapine. J Pharmacol Exp Ther 1996;276:658–666
32. Ring BJ, Binkley SN, Vandenbranden M, et al. In vitro interaction of the antipsychotic agent olanzapine with human cytochromes P450 CYP2C9, CYP2C19, CYP2D6, and CYP3A. Br J Clin Pharmacol 1996;41:181–186
33. Jann MW, Chang W-H, Davis CM, et al. Haloperidol and reduced haloperidol plasma levels in Chinese vs non-Chinese psychiatric patients. Psychiatry Res 1989;30:45–32
34. Chang W-H, Jann MW, Hwu H-G, et al. Ethnic comparison of haloperidol and reduced haloperidol plasma levels: Taiwan Chinese versus American non-Chinese. J Formos Med Assoc 1991;90:572–578
35. Jann MW, Grimsely S, Gray E, et al. Pharmacokinetics and pharmacodynamics of clozapine. Clin Pharmacokinet 1993;24:161–176
36. Haring C, Meise U, Humpel A, et al. Dose-related plasma levels of clozapine: influence of smoking behavior, sex, and age. Psychopharmacology (Berl) 1989;99(suppl):38–40
37. Anderson CB, True JE, Ereshefsky L, et al. Risperidone clinical efficacy: role of the metabolite 9-hydroxy-risperidone. In: Abstract of the New Clinical Drug Evaluation Unit Annual Meeting; June 1993; Boca Raton, Fla
38. Ereshefsky L, Anderson CB, True J, et al. Plasma concentration of oral risperidone and active metabolite in schizophrenics. In: Abstract of the American College of Clinical Pharmacy Meeting; August 1993; Reno, Nev
39. Huang ML, Van Peer A, Woestenborghs R, et al. Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. Clin Pharmacol Ther 1993;54:257–268
40. Shin SG, Chong WS, Jang U, et al. Association of risperidone metabolism with debrisoquine hydroxylation [abstract]. Presented at the 5th World Conference on Clinical Pharmacology and Therapeutics; July 1992; Yokohama, Japan

41. Anderson CB, True JE, Ereshefsky L, et al. Risperidone dose, plasma levels and response. Presented at the 146th Annual Meeting of the American Psychiatric Association; May 1993; San Francisco, Calif.
42. Fulton B, Goa KL. ICI-204,636: an initial appraisal of its pharmacological properties and clinical potential in the treatment of schizophrenia. CNS Drugs 1995;4:68–78.
43. Shimada E, Muraski M, Miura S, et al. A phase I study in healthy volunteers of ICI204636, a novel neuroleptic agent [abstract]. Int J Physiol Pharmacol 1994;44(suppl 1).
44. Fabre LF, Aravanitis L, Pultz J, et al. ICI 204,636 a novel atypical antipsychotic: early indication of safety and efficacy in patients with chronic and subchronic schizophrenia. Clin Ther 1995;17:366–378.
45. Hollister LE. Antipsychotic drugs. In: Hollister LE, ed. Clinical use of psychotherapeutic drugs. Springfield, Ill: Charles C. Thomas; 1973:13–55.
46. Ereshefsky L, Davis CM, Harrington CA, et al. Haloperidol and reduced haloperidol plasma levels in selected schizophrenic patients. J Clin Psychopharmacol 1984;4:138–142.
47. Ereshefsky L, Watanabe MD, Tran-Johnson T. Clozapine: an atypical antipsychotic. Clin Pharm 1989;8:691–709.
48. Jann MW, Ereshefsky L, Saklad SR, et al. Effects of carbamazepine on plasma haloperidol levels. J Clin Psychopharmacol 1985;5:106–109.
49. Kidron R, Averbuch I, Klein E, et al. Carbamazepine induction reduction of blood levels of haloperidol in chronic schizophrenia. Biol Psychiatry 1985;20:219–222.
50. Linnoila M, Viukari M, Vaisanen K, et al. Effect of anticonvulsants on plasma haloperidol and thioridazine levels. Am J Psychiatry 1980;137:819–821.
51. Miller D. Effects of phenytoin on plasma clozapine concentrations in two patients. J Clin Psychiatry 1991;52:23–25.
52. Jerling M, Lindstrom L, Bondesson U, et al. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine. Ther Drug Monit 1994;16:368–374.
53. Funderburg LG, Vertrees JE, True JE, et al. Seizure after the addition of erythromycin to clozapine treatment. Am J Psychiatry 1994;151:1840–1841.
54. Riskin TS. Effect of clozapine on plasma nortriptyline concentration. Pharmacopsychiatry 1994;27:41–42.
55. Jann MW, Saklad SR, Ereshefsky L, et al. Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. Psychopharmacology (Berl) 1986;90:468–470.
56. Ereshefsky L, Jann MW, Saklad SR, et al. Effects of smoking on fluphenazine clearance in psychiatric inpatients. Biol Psychiatry 1985;20:329–332.
57. Stimmel GL, Fallown IRH. Chlorpromazine plasma levels, adverse effects and tobacco smoking, case report. J Clin Psychiatry 1983;44:420–422.
58. Santos JL, Calabrianes JA, Almuqueira L, et al. Clinical implications of determination of plasma haloperidol levels. Acta Psychiatr Scand 1989;79:348–354.
59. Smith RC, Baumgarten R, Misra CH, et al. Haloperidol plasma levels and prolactin response as predictors of clinical improvement in schizophrenia. Arch Gen Psychiatry 1984;41:1044–1049.
60. Mavroidis ML, Kanter DR, Hirschowitz J. Clinical response and plasma levels in schizophrenia. Psychopharmacology (Berl) 1983;81:354–356.
61. Potkin SG, Shen Y, Zhou D, et al. Does a therapeutic window for plasma haloperidol exist? Psychopharmacol Bull 1985;21:59–61.
62. Volovka J, Cooper TB, Meisner M, et al. Haloperidol blood levels and effects in schizophrenia and schizoaffective disorders. Psychopharmacol Bull 1990;26:13–17.
63. Van Putten T, Marder SR, Wirshing WC, et al. Neuroleptic plasma levels: Schizophr Bull 1991;17:197–216.
64. Dysken MW, Javaid JI, Chang SS, et al. Fluphenazine pharmacokinetics and therapeutic response. Psychopharmacology (Berl) 1981;73:205–210.
65. Mavroidis ML, Kanter DR, Hirschowitz J. Fluphenazine plasma levels and clinical response. J Clin Psychiatry 1984;45:370–373.
66. Levinson DF, Simpson GM, Singh H, et al. Neuroleptic plasma level may predict response in patients who meet a criterion for improvement [letter]. Arch Gen Psychiatry 1988;45:877–879.
67. Perry PJ, Miller DD, Arndt SV. Clozapine and norclozapine concentrations and clinical response of treatment refractory patients. Am J Psychiatry 1991;148:231–235.
68. Jann MW, Ereshefsky L, Saklad SR, et al. Haloperidol and reduced haloperidol plasma levels in schizophrenic patients. Drug Intel Clin Pharm 1984;18:507.